REMARKS

Claims 7-17, 38-49, and 61-70 were pending in the application. Claims 7, 17, and 41 have been amended. New claims 71-92 have been added. Thus, claims 7-17, 38-49, and 61-92 are now pending.

Claims 7, 17, and 41 have been amended to correct for dependencies and formalities. Support for new claim 82 can be found throughout the specification, including at least at page 30, lines 17-18 and in the claims as originally filed. Support for new claims 71 and 85 can be found throughout the specification, including at least at page 20, lines 34-35 and page 28, lines 12-26, as well as ATCC Accession No. HB 11793. Support for new claims 72 and 86 can be found throughout the specification, at least at page 28, lines 18-26. Support for new claims 73, 81, 87 can be found throughout the specification, including at least at page 29, lines 31-33. Support for new claims 74, 79, and 88 can be found throughout the specification, including at least at page 20, lines 8-15 and lines 31-35. Support for new claims 75, 80, and 89 can be found throughout the specification, including at least at page 20, line 16 to page 21, line 26. Support for new claims 76 and 91 can be found throughout the specification, including at least at page 38, lines 14-15. Support for new claims 77 and 92 can be found throughout the specification, including at least at page 38, line 15 and at page 37, line 2. Support for new claims 78 and 90 can be found in the claims as originally filed and in the specification at least at page 22, lines 21-22. Support for new claims 83 and 84 can be found in the claims as originally filed and at page 26 of the specification. No new matter has been added.

Amendments to the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s).

Rejection of Claims 7-17, 38-49, and 61-70 Under 35 U.S.C. § 112, Second Paragraph

I. Rejection of Claim 7-17, 38-49, and 61-70 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 7-17, 38-49, and 61-70 under 35 U.S.C. § 112, second paragraph for recitation of the phrase "activating agent." The Examiner states that "it is unclear as to which products or molecules are to be encompassed by the phrase."

Applicant respectfully traverses the foregoing rejection on the grounds that claims 7-17, 38-49, and 61-70 particularly point out and distinctly claim the subject matter, which Applicant regards as the invention as required by 35 U.S.C. § 112, second paragraph. Applicant submits that based on the plain language of the claim and the teachings in Applicant's specification, claims 7-17, 38-49, and 61-70 are clear and definite to one of ordinary skill in the art.

Applicant notes that claims 7-17, 38-49, and 61-70 are directed to methods of treatment comprising administering "activating agents" specifically related to LT-β-R or "LT-β-R activating agents." Applicant defines the term "LT-β-R activating agent" in the specification as an agent which augments ligand binding to LT-β-R (as indicated by the Examiner), an agent which augments cell surface clustering of LT-β-R, or an agent which augments LT-β-R signaling (see page 10, lines 1-5 of the specification). Applicant provides numerous examples of LT-β-R activating agents, including IFN-γ, IFN-α, TNF, interferon inducing agents, and anti-LT-β-R antibodies, including BKA11, CDH10, BHA10, CBE11, and BCG6 (see page 10, lines 5-8 and page 22, lines 20-22 of the specification). Furthermore, Applicant teaches screening methods for identifying LT-β-R activating agents, wherein tumor cells are grown in the presence of a known LT-β-R activating agent, *e.g.*, IFN-γ, in the presence or absence of the LT-β-R activating agent being tested. The tumor cells are monitored for increased cell death, where the number of cells killed in the presence of the known LT-β-R activating agent is compared with the number obtained for the test LT-β-R activating agent (see page 21, line 27 to page 22, lines 18). An LT-β-R activating agent identified through this assay is one which "can potentiate the anti-tumor

activity of LT-α/β heteromeric complexes...in the presence of an LT-β-R activating agent such as IFN-γ" as determined through the measured optical density which is inversely proportional to the number of tumor cells killed. Thus, the term "LT-β-R activating agent" is clearly defined and supported by the teachings of the instant specification. Applicant respectfully requests that in view of the teachings of the specification, the rejection of claims 7-17, 38-49, and 61-70 under 35 U.S.C. § 112, second paragraph be withdrawn.

II. Rejection of Claim 7 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claim 7 (and claims that depend thereof) under 35 U.S.C. § 112, second paragraph for recitation of the phrase "reducing." The Examiner states that "it is a relative term of which there is no reference point from which to gauge a reduction." The Examiner also rejects claim 7 (and claims that depend thereof) for recitation of the phrase "severity" which the Examiner also asserts is a "relative term of which there is no reference point to gauge the amount."

Applicant respectfully traverses the foregoing rejection on the grounds that claim 7 (and claims that depend thereof) particularly points out and distinctly claims the subject matter, which Applicant regards as the invention as required by 35 U.S.C. § 112, second paragraph. Applicant submits that based on the plain language of the claim, *i.e.*, use the of phrases "reducing" and "severity ," and the teachings in Applicant's specification, claim 7 (and claims that depend thereof) is clear and definite to one of ordinary skill in the art.

Recitation of the term "reducing" is art-recognized and in the context of claim 7 is intended to mean any diminishment or lessening of neoplasia, evidenced by, for example, a diminishment in tumor size or tumor cell number. Applicant submits that the term "severity," is a term of art and in the context of claim 7 is intended to mean the negative condition wherein cells are neoplastic and, therefore, are capable of forming a tumor and growing in later stages of tumorigenesis. Applicant submits that one of ordinary skill in the art would recognize that the

term "severity," as used in claim 7, indicates anything less than continued neoplastic growth, *i.e.*, inhibition of tumor growth or formation. Applicant provides examples of a reduction in the severity of neoplasia at page 30, line 4 to page 31, line 29 of the specification. Applicant teaches that treatment of mice inoculated with WiDr human adenocarcinoma cells with the anti-LT-β-R antibody CBE11 either in conjunction with the injection of tumor cells or following tumor formation, blocked tumor formation and inhibited tumor growth, respectively. Thus, Applicant teaches that these experiments demonstrate that an anti-LT-β-R antibody can effectually inhibit tumor formation at the initial stages (evidenced in those mice co-injected with tumor cells and CBE11) and can also block tumor cell growth during tumorigenesis (evidenced in those mice injected with tumor cells and later treated with CBE11). These experiments demonstrate that administration of a single LT-β-R activating agent, e.g., CBE11. can effectively treat or reduce the advancement, severity or effects of neoplasia in an affected animal (page 31, lines 23-29 of the specification).

The Examiner also rejects claim 7 and claims that depend thereof under 35 U.S.C. § 112, second paragraph for recitation of the phrase "effective amount." The Examiner states that "it is unclear from the specification as to what this amount is intended to encompass." Recitation of the term "effective amount" is art-recognized and is intended to mean an amount sufficient to effect beneficial or desired results as set forth in Applicant's claims, for example, treating or reducing the advancement, severity or effects of neoplasia. Applicant submits that the determination of a particular pharmaceutical formulation and therapeutically effective dosage for a given indication would be understood by those of skill in the art based on Applicant's teachings. For example, as described in the specification at page 33, line 35, factors that are considered for making such determination by those of ordinary skill in the art include the condition and weight of the patient, the extent of the desired treatment and the tolerance of the patient for the treatment.

In view of the above, Applicant submits that the terms "reducing," "severity," and "effective amount" are clear and definite and well understood by those of ordinary skill in the art.

III. Rejection of Claim 8 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claim 8 under 35 U.S.C. § 112, second paragraph for use the phrase "LT-α/β heteromeric complex" without antecedent basis. Applicant respectfully traverses the foregoing rejection on the grounds that claim 8 does not recite the term "LT-α/β heteromeric complex." Thus, Applicant respectfully requests that the Examiner withdraw the 35 U.S.C. § 112, second paragraph rejection of claim 8.

IV. Rejection of Claim 17 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claim 17 under 35 U.S.C. § 112, second paragraph for depending from claim 6 which has been canceled. Applicant has amended claim 17 to depend from claims 7-17, thus rendering the rejection moot.

V. Rejection of Claim 49 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claim 49 under 35 U.S.C. § 112, second paragraph for being "indefinite because it is unclear as to which claim it depends." Claim 49 depends from claims 41-48. Applicant has amended claim 41 to depend from claim 38 instead of canceled claim 37. Applicant submits that in accordance with 37 C.F.R. 1.75, claim 49 is clear and definite in view of the amendment to claim 41. Thus, Applicant respectfully requests that the Examiner withdraw the rejection of claim 49.

Accordingly, Applicant respectfully requests that in view of the amendments to the claims and the reasons described above, the rejection of claims 7-17, 38-49, and 61-70 under section 112, second paragraph be reconsidered and withdrawn.

Rejection of Claims 7-17, 38-49, and 61-70 under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 7-17, 38-49, and 61-70 under 35 U.S.C. § 112, first paragraph. The Examiner states that the specification does not enable one of ordinary skill in the art to "treat neoplasia in general in a subject comprising the administration of any LT-β-R activating agents, and a pharmaceutical composition comprising LT-β-R activating agents." Applicant respectfully traverses this rejection.

The pending claims are directed to a method for treating or reducing the advancement, severity or effects of neoplasia comprising administering a therapeutically effective amount of compositions, each composition comprising at least one LT-β-R activating agent and a pharmaceutically acceptable carrier, ***wherein at least one LT-β-R activating agent comprises an anti-LT-β-R antibody***. The claimed invention is also directed to a pharmaceutical composition comprising a therapeutically effective amount of at least two LT-β-R activating agents, and a pharmaceutically acceptable carrier, ***wherein at least one LT-β-R activating agent comprises an anti-LT-β-R antibody***. The claimed invention is further directed to a method for treating or reducing the advancement, severity or effects of neoplasia comprising administering an effective amount of a pharmaceutical composition comprising ***an anti-LT-β-R antibody*** and a pharmaceutically acceptable carrier, wherein the composition ***is administered in the presence of an exogenous LT-β-R activating agent***.

The Examiner acknowledges that the specification is "enabling for a method of treating colon carcinoma in a host and testing cytotoxic effects of a compound in an in vitro system comprising the administration of a LT-α/β heteromeric complex, a LT-β-R activating antibody, selected from BKA11 and CDH10, and IFN-γ, and a pharmaceutical composition comprising a LT-β-R activating antibody, selected from BKA11 and CDH10, and IFN-γ." The Examiner states, however, that the specification does not teach "any other types of agents that are able to

activate LT-β-R, and further that the specification does not enable a method of treating neoplasia. Applicant respectfully traverses this rejection.

Applicant submits that the instant specification fully enables one of ordinary skill in the art to treat neoplasia as claimed, as well as to make and use the pharmaceutical compositions within the scope of the presently pending claims. As described above, the claims recite that ***at least one LT-β-R activating agent comprises an anti-LT-β-R antibody***. The claims, therefore, are not as broad as recited by the Examiner. Applicant submits that the teachings of the specification are commensurate with the scope of the claims.

Applicant teaches how to make and use anti-LT-β-R antibodies which can be used in combination with additional LT-β-R activating agents. For example, at page 19, line 14 to page 21, line 26 of the instant specification, Applicant provides examples of different types of anti-LT-β-R antibodies and teaches how to make them. Applicant teaches that monoclonal antibodies against LT-β-R can be made by injecting mice with a human LT-β-R Fc fusion protein. Applicant also teaches how to make recombinant LT-β-R antibodies, such as chimeric and humanized antibodies, which can be used in the claimed invention. The specification also teaches how to identify antibodies with LT-β-R activating activity, *i.e.*, anti-tumor activity. Applicants describe screening methods, wherein anti-LT-β-R antibodies are evaluated for their ability to kill tumor cells (page 21, line 27 to page 22, line 22). Thus, Applicant submits that the specification has provided sufficient guidance to the ordinarily skilled artisan to make and use the invention and identify LT-β-R activating agents, including anti-LT-β-R antibodies, with predictability and without undue experimentation.

Applicant has also provided ample guidance to enable one of ordinary skill in the art to make and use additional LT-β-R activating agents, including, but not limited to, IFN-γ, IFN-α, TNF, interferon inducing agents. Applicant also provides examples of anti-LT-β-R antibodies, including BKA11, CDH10, BHA10, CBE11, and BCG6 (see page 10, lines 5-8 and page 22, lines 20-22 of the specification). As well as teaching examples of LT-β-R activating agents,

Applicant also teaches screening assays for identifying said agents, as described above and at page 21, line 27, to page 22, line 22 of the specification. Applicant teaches that LT-β-R blocking agents can be identified using screening methods that detect the ability of the agent to facilitate tumor cell death. Thus, Applicant points out that the specification provides ample guidance to enable one of ordinary skill in the art to make and use the second LT-β-R activating agent of the invention with predictability and without undue experimentation.

Finally, Applicant describes in the instant specification the claimed combination of an anti-LT-β-R antibody and a second LT-β-R activating agent. Applicant teaches *in vivo* and *in vitro* assays which can be used to identify LT-β-R activating agents which function alone or in combination to inhibit tumor cell growth. Applicant provides working examples which demonstrate the claimed method for treating or reducing the advancement, severity or effects of neoplasia ,including, but not limited to, adenocarcinoma, comprising administering a at least two LT-β-R activating agents, wherein at least one LT-β-R activating agent comprises an anti-LT-β-R antibody. For example, Applicant teaches an *in vitro* assay where an anti-LT-β-R antibody is tested in combination with a second LT-β-R activating agent for a combined cytotoxic effect on tumor cells. In Example 8 and Figure 5 of the specification (pages 44-46), Applicant describes results from an HT29 cytolytic assay where tumor cells are exposed to anti-LT-β-R antibodies alone or in combination. Applicant teaches that combinations of anti-LT-β-R antibodies significantly increases death of tumor cells in comparison to treatment of HT29 cells with anti-LT-β-R antibodies alone. The results shown in Figure 5 provide clear evidence that a combination of at least two LT-β-R activating agents can effectively kill tumor cells.

Applicant also describes an *in vivo* working example which demonstrates that an anti-LT-β-R antibody effectively inhibits tumor growth in combination with an LT-β-R activating agent (page 31, lines 8-20 and Example 14). Applicant demonstrates that tumor cells injected into mice co-administered with the combination of an anti-LT-β-R antibody and a second LT-β-R activating agent, show a significant decrease in tumor volume compared to control mice.

Example 14 of the specification also demonstrates that administration of the combination of an anti-LT-β-R antibody and a second LT-β-R activating agent to mice with developed tumors causes a decrease in tumor volume. As described above, based on the teachings of each LT-β-R activating agent alone and the teachings of combinations of LT-β-R activating agents, the specification has provided sufficient guidance to the ordinarily skilled artisan to make and use the combinations of the invention without undue experimentation.

Applicant submits that the data presented in the Example section of the specification supports the claimed invention, and therapeutic uses thereof, and should not be used to limit the scope of the claimed invention. The LT-β-R activating agents described in the working example are representative of the claimed LT-β-R activating agents described in the specification. Furthermore, the SCID/WiDr murine model taught in the specification is representative of neoplasia in general and should not be used to limit the claimed invention as suggested by the Examiner. In order to meet the enablement requirement, it is not necessary that a patent specification include specific examples of every different embodiment encompassed by the claims. Furthermore, the enablement requirement is satisfied if the specification contains sufficient information regarding the subject matter of the claims to enable one of ordinary skill in the art to make and use the claimed invention without undue experimentation (MPEP 2164).

The Examiner provides Hipp *et al.* in support of the notion that "it is a well accepted fact that the treatment of cancer is often unpredictable and strategies to overcome tumor progression still need to be thoroughly investigated." Hipp *et al.* is a review of the state of the art with respect to cancer vaccines. Applicant respectfully points out that the claimed invention is not directed to a cancer vaccine, but rather is directed to ***treating or reducing the advancement, severity or effects of neoplasia***. Applicants also point out that antibodies have been approved for the treatment of cancers, thus exemplifying the predictability of the success of the claimed invention. For example, therapeutic antibodies such as Rituximab or Rituxan have been approved by the FDA for treatment of various neoplasia. In another example, Cetuximab by

Imclone was advanced in development as a cancer therapy and is currently entering a Phase III clinical study (see www.Cetuximab.com).

The Examiner also cites Jain *et al.* with regard to the statement that "[b]ecause cancers are derived from different cell types, they require different modalities of treatment." Jain teaches challenges encountered with drug delivery to tumors, and provides strategies for overcoming such issues. Applicant submits that Jain *et al.*, which was published in 1990, is not representative of the predictability of cancer therapies. As stated herein, therapeutic antibodies, such as Rituximab and Cetuximab, have been proven useful as cancer therapies, thus supporting the predictability of such therapies. Furthermore, Applicant teaches various modes of administration of the compositions of the claimed invention, which depend, at least in part, on the cell or tissue type being treated (pages 32-37 of the specification). One of ordinary skill in the art would recognize that the best mode of delivery of the claimed invention depends on the type of neoplasia being treated or reduced.

Applicant maintains that the specification fully enables one of ordinary skill in the art to make and use the claimed invention, and respectfully request that the Examiner withdraw the 112, first paragraph rejection.

CONCLUSION

Reconsideration and allowance of all the pending claims is respectfully requested. If a telephone conversation with Applicant's Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,

Elizabeth A. Hanley, Esq.
Registration No. 33,505
for
Amy E. Mandragouras, Esq.
Registration No. 36,207
Attorney for Applicant

LAHIVE & COCKFIELD, LLP
28 State Street
Boston, MA 02109
(617) 227-7400
Dated: September 26, 2003